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FOLEY & LARDNER
SUITE 500
3000 K ST N.W.
WASHINGTON, D.C. 20007-5109

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☑ Responsive to communication filed on Sept 14, 1994 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-15 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☑ Claims 1-15 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

Applicant's request for the removal of finality in the office action mailed May 27, 1994 has been considered. Finality has been removed and the points raised by applicant are addressed below. In summary applicant has requested more explanation as to why the submitted references do not overcome the deposit requirement and applicant argued that the Velander declaration filed in 07/638,995 is proper for consideration in the instant application.

> 35 U.S.C. § 101 reads as follows:
> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 11 is rejected under 35 U.S.C. § 101 because it is drawn to non-statutory subject matter. Claim 11 is drawn to a method of producing transgenic animals, which includes humans. Claims to a method to produce transgenic humans is non-statutory.

Applicant's amendment has overcome the rejection, but applicant has requested a citation. Applicant is referred to 1118 OG 19 April 7, 1987, 370 1122 TMOG.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification remains objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure. Claims 1-15 are drawn to a non-human transgenic mammal which secretes protein C into its milk, where the expression of the

genomic protein C DNA sequences is regulated by the Sau3A-Kpn1 fragment of the mouse whey acidic protein promoter operatively linked to a genomic fragment of human protein C where said fragment begins 21 basepairs 5' to the initiation codon of protein C to the NheI site 3' to the termination codon, a process for producing said transgenic mammals and a process of producing protein C by isolation from the milk of the transgenic mammal. Therefore, DNA sequences which encode protein C and protein C non-coding regions appear to be critical elements for the instant invention. However, the specification does not identify a readily available and reproducible source for these critical elements. This deposit requirement has been made in view of the following scope limitation. Moreover, applicant is limited to transgenic mice and transgenic pigs where the transgene is human protein C DNA sequences contained in the Eco RI fragment of WAPpC1 and WAPpC2 regulated by the mouse wheys acidic protein promoter, or where the transgene is the Sau3A-Kpn1 fragment of the mouse whey acidic protein promoter operatively linked to a genomic fragment of human protein C where said fragment begins 21 basepairs 5' to the initiation codon of protein C to the NheI site 3' to the termination codon, a process for producing said transgenic mice and a process of producing protein C by isolation from the milk of said transgenic mice. Applicant has not enable the production of all transgenic mammals which produce heterologous protein C in their milk. The production of transgenic mammals which exhibit

tissue specific production of a specific protein is unpredictable. Applicant has not taught nor provided evidence that protein C DNA sequences will integrate into the genome of all mammals and that such integration will permit the production of heterologous protein C in the milk of all mammals. Thus, the skilled artisan is not provided with a reasonable expectation of success and without an undue amount of experimentation in the implementation of the invention of claims 1-15.

Applicant argues that the specification does contain an adequate written description and an enabling disclosure. Applicant continues to state that the rejection addresses a lack of enablement and argues the rejection on the basis of enablement. Applicant argues that the protein C encoding DNA's are well known and readily available. In support applicant states that DNA for human protein C is available through the NRRL, accession number B15926, US Patent 4,775,642 and a variety of journal articles. Applicant also argues that the techniques for isolating genomic clones and producing expression constructs are known in the art. Applicant argues that integration of DNA sequences into host cells by microinjection, is observed universally in vitro and in vivo. Applicant argues that a species can enable a genus; that all specifies do not need to be exemplified. Applicant argues that Puhler discloses the production of transgenic animals which express a variety of proteins from the whey acidic protein promoter. Applicant argue

that the declaration of Velander of record in 07/636,995 supports the enablement of mice and pigs, and therefore all mammals in the production of human protein C in milk. Applicant argues that the production of mutant promoters and protein C can be produced by techniques well known in the art. Applicant argues that silent mutations in protein C will behave as the protein C DNA sequence exemplified. Applicant argues that the functional domains of protein C are known in the art so that mutations in these site could be readily produced by the artisan. These arguments are not persuasive. It is pointed out to applicant that upon reconsideration, the rejection under 35 USC 112 it directed to the lack of enabling disclosure. Any references to the written description are an attempt to answer applicant's response filed February 18, 1993. These have been removed. The specification defines only one DNA sequence as having protein C activity, and as such lacks an enabling disclosure for these DNA sequences. In addition there is no disclosure in the specification to determine those DNA sequences which have protein C activity. Applicant has not clearly defined a DNA sequence encoding a protein having protein C activity. For example, it can not be discerned if applicant is referring to any and all proteins which have protein C enzymatic activity or protein C substrate binding activity. In addition it is not clear from applicant's specification if by protein C activity it is meant a protein with the enzymatic activity of protein C, but lacking one or more of the structural

features associated with the protein. Applicant has not supplied a definition of "having protein C activity" within the specification of the instant applicant so that the artisan will realize which protein or proteins they mean. By not defining "protein C activity", applicant's scope is limited to the specific embodiment. The references supplied by applicant does not provide a definition of protein C activity that is accepted in the art. For example, US Patent 4,968,626 describes protein C has being characterized as having anticoagulant and fibrinolytic activity (col. 3, lines 9-11 in exhibit 1). The protein is also described as being a single chain polypeptide which undergoes process to give rise to a two-chain, disulfide bonded protein (col. 3, lines 29-33 in exhibit 1). Protein C is stated to contain carbohydrate moieties (col. 4, line 62 to col. 5, line 2 exhibit 1). The catalytic domains are described as residing in exons VII and VIII (col. 5, lines 3-5 in exhibit 1). In US Patent 4,959,318, there is discussion of hybrid proteins where the domains of vitamin K dependent plasma proteins, of protein C is a member, are interchanged to produce a protein with a particular enzymatic activity but with calcium binding domains or carbohydrate modification domains from other vitamin K plasma proteins (col. 7, line 44 to col. 8, line 4 in exhibit 2). Thus it is not clear if a DNA sequence having protein C activity would, according to applicant's disclosure, need to have both the anticoagulant and fibrinolytic activities, which are separate

(Plutzky, page 546, col. 1, lines 3-7 in exhibit 3). It is also not clear which protein C modifications a DNA sequence encoding a protein having protein C activity would have to possess. Applicant has not offered a definition of "protein C" or a "DNA encoding a protein having protein C activity" which indicates the enzymatic activity or the substrate binding activity in conjunction with post-translational modifications contained or possessed by "protein C" or "protein C activity". Applicant through the specific embodiment has enabled only one DNA sequence encoding a protein encoding protein C activity. In this same regard, applicant has not provided guidelines for determining DNA sequences encoding mutant protein C activity. The specification does not provide a description of the mutations, the type of mutation or where they occur in the DNA or amino acid sequence of protein C. The assays disclosed in the specification do not provide support for identifying mutations in the absence of further guidelines in the specification. Further, a reproducible and readily available source to the public for the DNA sequence which encodes protein C activity in the specific embodiment has not been provided in the specification. The specification lists an individual as the supplier of the DNA sequence for the production of transgenic mice and pigs producing protein C in their milk. This is not a reproducible source any guarantees in the form of a deposit are made only between applicant or applicant's representative and the Patent Office. A third party

is currently unacceptable in this type of agreement. It is not known how the DNA sequence used by applicant relates to those known in the art. For example, this particular DNA sequence could have a mutation or mutations in the protein C amino acid sequence which alters one or more of the post-translational modification. Therefore DNA sequences for human protein C available through the NRRL, accession number B15926, US Patent 4,775,642 and a variety of journal articles is not a reproducible source because it can not be determined how they are similar or dissimilar to the DNA of the instant disclosure. Thus the deposit requirement was rightfully stated to be need for the enablement of the claims as the scope limitation set forth. In the production of transgenic mammals integration is a necessary prerequisite to expression of the transgene as protein. The examiner's rejection in the office action of July 22, 1993, page 7, lines 6-11 is to a relationship between integration and production of protein. The protein C DNA sequence may integrate but not be expressed as protein. The integration may be near silencers such that there is no expression or very little production of protein C. The Puhler article lists several proteins produced in transgenic mice and one protein produced in transgenic pigs where expression of the transgene is from the whey acidic acid protein promoter (pages 139-140, table 11). This is not seen as evidence that the whey acidic protein promoter would be expected to be recognized in all mammals or that the expression of human protein C DNA sequences

would be expected to be in any mammal. The pig expressed growth hormone which is a protein unrelated to protein C as the growth hormone does not require post-translational modifications for activity. While the promoter may be recognized in pigs, the promoter-DNA sequence construct may not be situated such that expression would occur. Only one example of protein C production in transgenic mice is observed. The art recognizes that the whey acidic protein promoter does not universally promote transgene expression even in transgenic mice (Tomaserto, abstract, lines 11-13). Thus there is not universal recognition of the whey acidic protein promoter even in mice The information in the Velander declaration filed in 07/636995 has been convincing for a scope of transgenic pigs, as well as the original scope of transgenic mice. Velander, in the declaration and accompanying reference, made transgenic pigs which expressed protein C in their milk using the same constructs as the transgenic mice and pigs of the specification. Thus, as applicant has not defined " a DNA sequence encoding a protein having protein C activity", and have not provided guidelines for determining such a DNA sequence, applicant's are therefore permitted a scope limitation to this particular DNA sequence. Different DNA sequences are subject to different susceptibilities to nucleases, different sites of integration and different levels of expression (Palmiter (1986) Ann. Rev. Genet. 20, 465-499, page 473, lines 3-8 and page 480, lines 4-9 and page 481, parag. 2, lines 1-2).

Claims 1-15 remain rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification in the previous office action.

Claims 1-15 remain rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for reasons stated in the previous office action. Claims 1,3,6,11,12 and 14 contain the term "comprises substantially" or "substantially comprising" which is vague and indefinite as the reader can not be sure of other components of the promoter sequence. "Substantially" has no clear definition is the art and is open to broad interpretations. "Comprises" is open ended claim language. Thus the term "comprises substantially" or variations thereof, read as though the promoter sequence contains critical but unclaimed characteristics. In this regard the term is vague and indefinite by not defining the metes and bounds of the claims. Claim 3 is vague and indefinite as the term "variant thereof" is not defined in the claim or specification. It can not be discerned if applicant means a structural or activity variant or some other type of variant.

Applicant argues that "substantially" and "variant thereof" are set forth so that the artisan would realize the metes and bounds of the claims. This argument is not persuasive. Both terms

are broad in interpretation. At the pages cited by applicant definitions are not provided for "substantially" and "variant thereof".

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-10 and 12-15 remain rejected under 35 U.S.C. § 103 as being unpatentable over Pittius et. al. (1988) Proced. Natl. Acad. Sci. 85, 5874-5878 in view of Grinnell et. al. (1987) Bio/Technology 5, 1189-1192, Brinster et al (1988) Proced. Natl. Acad. Sci. 85, 836-840, Campbell et al (1984) Nucl. Acids Res. 12, 8686-8697 and Clark et al (1987) TIBTECH 5, 20-24 for the reasons of record. Pittius teaches that tPA can be detected in the milk of a transgenic mouse, when expression of the tPA transgene is regulated by the mouse whey acidic protein promoter and the tPA transgene contains a signal peptide which directs

secretion of the protein product into the milk (page 5875, col. 3, parag. 1, line 1 to page 5876, col. 2, through parag. 2 and page 5876, fig. 2). Grinnell teaches the expression of human protein C in tissue culture cells transfected with an expression vector comprised of the cDNA for human protein C and regulatory sequences, where active protein C was isolated from the culture media (page 1191, col. 2, parag. 1). Brinster teaches that the inclusion of intron sequences enhances the expression of a transgene in transgenic mice (see abstract and page 837, fig. 1). Campbell teaches the genomic sequence for mouse protein C (see pages 8691-8692, fig. 3). Clark teaches the production of compounds of pharmaceutical importance in transgenic mammals by the specific expression of DNA sequences which encode a compound of interest in the mammary gland of the transgenic mammal, the secretion of the compound into the milk of the mammal and the subsequent isolation of the compound from the milk (page 22, col. 1, parag. 2 to col. 2, line 13).

Applicant argues that Pittius is not a proper 103 rejection as tPA does not require gamma carboxylation as does protein C and tPA is processed in cells by proteolytic cleavage. Applicant also argues that although both tPA and protein C are glycosylated, the glycosylations are different and require different enzymes. Applicant argues that gamma carboxylation is required for protein C activity and that gamma carboxylation is not required for tPA activity. Applicant also argues that protein C requires ß-

hydroxylation which tPA does not. In addition applicant argues that tPA was cleaved by enzymes in mammary cells and that this would have been an indication that protein C would have undergo inappropriate degradation in transgenic milk. Applicant argues that the data presented in Grinnell (1987) for protein C production in vitro would have motivated the production of protein C in kidney of transgenic mice in view of Grinnell (1990). Grinnell (1990) teaches that mammary gland epithelial cell cultures were the worst in the production of protein C, where kidney cells were the best. Applicant argues that mammary cells have limited capacity in vitro for gamma carboxylation and that kidney, based on in vitro data, would have been the organ of choice. Applicant also submitted publications that indicate that to be useful protein C in vitro production needs to be 10pg protein C/cell/day (Yan) or 10ug protein C/ml/day (Grinnell (1990). Applicant in addition argues that Brinster teaches at most that some introns can increase expression in transgenic animals. Applicant argues that Brinster recognizes some predictability in the effect of introns on transgene expression. Furthermore applicant argues that Clark is not proper as it is not directly addresses to the production of protein C in the milk of transgenic animals. These arguments are not persuasive. When the cited art is reviewed together a reasonable expectation of success is provided the ordinary artisan. Pittius teaches that the transgenic mice produce 50ug tPA/ml of milk. This clearly

supersedes the cited art reference to a useful production rate. Of course this is not an accurate comparison as it is not possible to compare in vitro and in vivo results as in Yan and Grinnell. However, Pittius did consider these result for the production of tPA in transgenic mice sufficient motivation for the transfer of the technology to dairy animals depending on advances in understanding of mammary gland expression (page 5878, col. 1, lines 5-11). The Examiner did not find in Pittius that the presence of enzymes in the mammary gland or milk presented a problem for the production of tPA. It would be helpful for applicant to point to specific page and lines for critical arguments. It appears from applicant's arguments that applicant believes that artisan would not be motivated to produce transgenic mice for the production of protein C because of reports by Grinnell (1990) that in vitro mammary epithelium is not efficient in the production of protein C. While Grinnell (1990) submitted by applicant teaches away from the expression of protein C in mammary gland epithelial cell culture, an in vitro situation, it does not teach away from the in vivo situation of Pittius in view of Grinnell (1987). The specific post translational modifications required for protein C would have been assumed to be present in mammary gland as Grinnell (1990) indicates the production of some functional protein C in mammary gland tissue culture cells (Grinnell (1990) page 31, lines 4-8). Pittius teaching that heterologous proteins expressed in the

mammary gland of transgenic mice are post-translationally modified in view of Grinnell (1987) teaching the expression of fully active protein C in tissue culture cells (page 1191, col.1, text lines 6-8) provides a reasonable expectation of success that protein C expressed in the mammary gland of transgenic mice will also be so modified to have functional activity. Brinster clear teaches that expression of both rat growth hormone and human ß-globin DNA sequences in transgenic mice were increased when an intron was present in the construct (page 839, figs. 3 and 4, page 839, col. 2, "Discussion", parag. 1, lines 1-5 and page 840, col. 1, parag. 5 to col. 2, line 2). It is not seen wear Brinster teaches that the additions of introns is unpredictable. The general teachings of Clark to the production of blood proteins in the mammary gland of transgenic farm animals provide sufficient motivation to adapt a transgenic protocol to the mammary gland of the larger and therefore more cost effective animal. The fact that Clark teaches that proteases in the milk may present a problem in stability does not teach away from the motivation provided. In fact Clark states that as blood proteins naturally occur in a milieu of proteases in the blood stream, the environment of bovine or ovine milk would indicate not adversely affect the stability of the blood proteins secreted into the milk of transgenic farm animals. Clark also states that blood proteins are found in the milk of wild type animals, indicating the feasibility producing blood proteins in the mammary gland of

transgenic farm animals (Clark, page 23, col. 1, parag. 5 to col. 2, line 12). The teachings of Grinnell (1987) in view of Pittius and Clark provide motivation for the production of pharmaceutical of interest in the milk of transgenic animals in order to obtain commercially useful quantities of the pharmaceutical.

Claim 11 remains rejected under 35 U.S.C. § 103 as being unpatentable over Colpan et. al. (1984) Journal of Chromatography 296, 339-353 in view of Hogan et. al. (1986) Manipulation of the Mouse Embryo, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY. pages 153-203 for the reasons of record. Colpan teaches the purification of plasmid DNA by anion exchange HPLC. Hogan states that DNA for the production of transgenic animals must free of contaminants which may harm the egg. New uses for known methods do not necessarily overcome the art in the absence of unexpected results.

Applicant argues that Hogan teaches that deleterious impurities must be removed from the DNA to be used to make transgenic animals, but Hogan does not teach the method of Colpan given that Colpan predates Hogan. Applicant argues that Hogan actually teaches against Colpan in not teaching Colpan's method. Applicant argues that Colpan does not teach purifying DNA molecules by anion exchange HPLC for the production of transgenic animals. Applicant also argues that their is no motivation for the artisan in using Colpan. Applicant also argues that Hogan in view of Colpan does not suggest purifying the DNA construct of

the WAP promoter and DNA sequences encoding protein C. These arguments are not persuasive. Hogan in teaching that the DNA construct to be used as the transgene must be purified from contaminants is sufficient motivation for any method known in the art at the time of filing to purify DNA. Colpan is such a teaching. The publication dates of Colpan and Hogan in reference to each other is not a condition under 35 USC 103. The particular DNA construct being purified is obvious in the absence of results to the contrary.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Dr. D. Crouch
October 20, 1994

Elizabeth C. Weimar

ELIZABETH C. WEIMAR
SUPERVISORY PATENT EXAMINER
ART UNIT 184